10/599,824 Compounds

~~10/513699~~

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSPTAEAL1624

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	JUL 02	LMEDLINE coverage updated
NEWS 3	JUL 02	SCISEARCH enhanced with complete author names
NEWS 4	JUL 02	CHEMCATS accession numbers revised
NEWS 5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
NEWS 8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 9	JUL 30	USGENE now available on STN
NEWS 10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 11	AUG 06	BEILSTEIN updated with new compounds
NEWS 12	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 13	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 14	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 15	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 16	AUG 27	USPATOLD now available on STN
NEWS 17	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 18	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 19	SEP 13	FORIS renamed to SOFIS
NEWS 20	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 21	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 22	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 23	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific

<12/04/2007> Erich Leese

research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:41:51 ON 24 SEP 2007

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 16:41:58 ON 24 SEP 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1
DICTIONARY FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

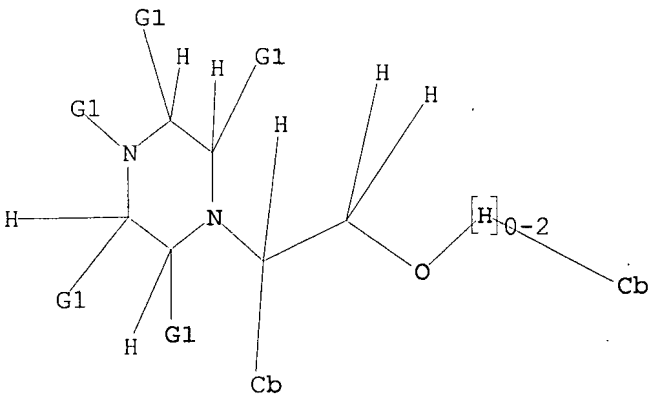
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\Stnexp\Queries\10599824.str

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 H,X,Ak,O

Structure attributes must be viewed using STN Express query preparation.

=> s l1 full
FULL SEARCH INITIATED 16:42:20 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 258294 TO ITERATE

100.0% PROCESSED 258294 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.04

L2 1 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	172.10	172.31

FILE 'CAPLUS' ENTERED AT 16:42:31 ON 24 SEP 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 24 Sep 2007 VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007 (20070923/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

```
=> s l1 full
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.



FULL SEARCH INITIATED 16:42:39 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   258294 TO ITERATE

100.0% PROCESSED   258294 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.04

L3             1 SEA SSS FUL L1



L4             1 L3

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.47     345.35

FILE 'CAPLUS' ENTERED AT 16:42:49 ON 24 SEP 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 24 Sep 2007  VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007  (20070923/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s l2 full
L5             1 L2

=> d ibib abs

L5   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:589533  CAPLUS
DOCUMENT NUMBER:          141:140464
TITLE:                    N-(substituted arylmethyl)-4-(disubstituted
```

methyl)piperidines and piperazines

INVENTOR(S): Ding, Ping; Henrie, Robert N., II; Cohen, Daniel H.; Lyga, John W.; Rosen, David S.; Theodoridis, George; Zhang, Qun; Yeager, Walter H.; Donovan, Stephen F.; Zhang, Steven Shunxiang; Shulman, Inna; Yu, Seong Jae; Wnag, Gouzhi; Zhang, Y. Larry; Gopalsamy, Ariamala; Warkentin, Dennis L.; Rensner, Paul E.; Silverman, Ian R.; Cullen, Thomas G.

PATENT ASSIGNEE(S): FMC Corporation, USA

SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

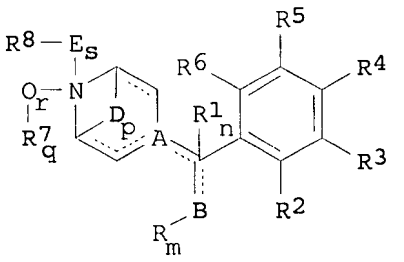
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

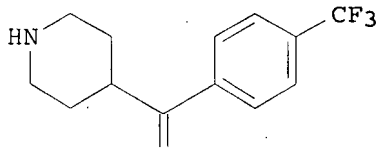
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004060865	A2	20040722	WO 2003-US39046		20031208
WO 2004060865	A3	20041104			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2003296373	A1	20040729	AU 2003-296373		20031208
EP 1572668	A2	20050914	EP 2003-814673		20031208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003016747	A	20051018	BR 2003-16747		20031208
CN 1729178	A	20060201	CN 2003-80106750		20031208
CN 1744895	A	20060308	CN 2003-80109445		20031208
JP 2006511621	T	20060406	JP 2005-508564		20031208
IN 2005DN02489	A	20061229	IN 2005-DN2489		20050609
IN 2005DN02485	A	20070427	IN 2005-DN2485		20050609
ZA 2005004870	A	20060426	ZA 2005-4870		20050614
ZA 2005004871	A	20060426	ZA 2005-4871		20050614
MX 2005PA06426	A	20050908	MX 2005-PA6426		20050615
US 2006166962	A1	20060727	US 2006-538997		20060208
PRIORITY APPLN. INFO.:			US 2002-434718P	P	20021218
			US 2003-495059P	P	20030814
			WO 2003-US39046	W	20031208

OTHER SOURCE(S): MARPAT 141:140464

GI



I

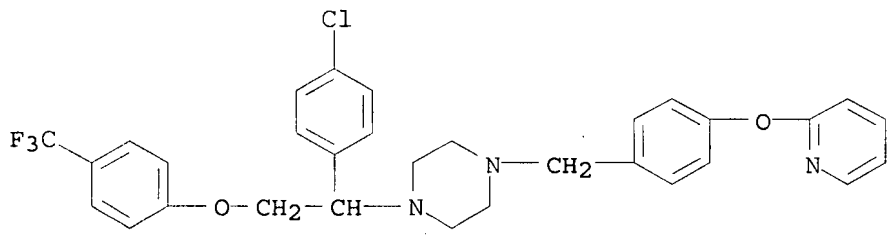


II

AB Title compds. I [m, n, q, r, s = 0-1; p = 0-3; A = CH, N forming a 6-membered azine ring selected from piperidine or piperazine; R2-6 = H, halo, alkyl, etc.; B = O; with provisions] are prepared For instance, 4-bromobenzotrifluoride is transmetalated (THF, n-BuLi, -75°) and treated with tert-Bu 4-[N-methoxy-N-methylcarbamoyl]piperidine-1-carboxylate to give tert-Bu 4-[(4-(trifluoromethyl)phenyl)carbonyl]piperidine-1-carboxylate. This intermediate is deprotected to give II. II gave 100% mortality and 100% growth inhibition of tobacco budworms.

=> d hitstr

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
IT 725231-94-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(N-(substituted arylmethyl)-4-(disubstituted methyl)piperidines and piperazines)
RN 725231-94-7 CAPLUS
CN Piperazine, 1-[1-(4-chlorophenyl)-2-[4-(trifluoromethyl)phenoxy]ethyl]-4-[[4-(2-pyridinyloxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	8.56	353.91

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.78	-0.78

FILE 'REGISTRY' ENTERED AT 16:47:02 ON 24 SEP 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

<12/04/2007> Erich Leese

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1
DICTIONARY FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

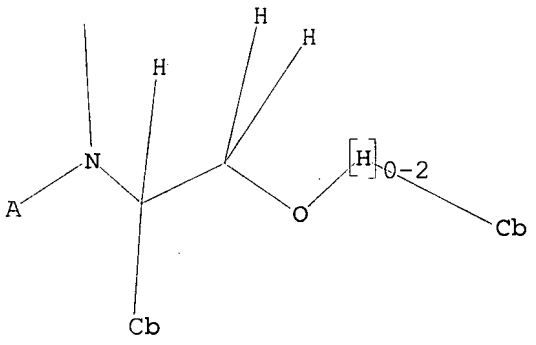
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\Stnexp\Queries\10599824broad.str

L6 STRUCTURE UPLOADED

=> d l6
L6 HAS NO ANSWERS
L6 STR



G1 H,X,Ak,O

Structure attributes must be viewed using STN Express query preparation.

=> s l6 full
FULL SEARCH INITIATED 16:50:46 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 6037621 TO ITERATE

8.6% PROCESSED 516823 ITERATIONS 7 ANSWERS

15.8% PROCESSED 955056 ITERATIONS 7 ANSWERS

16.6% PROCESSED 1000000 ITERATIONS 7 ANSWERS

<12/04/2007> Erich Leese

INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.39

FULL FILE PROJECTIONS: ONLINE **INCOMPLETE**
BATCH **INCOMPLETE**
PROJECTED ITERATIONS: 6037621 TO 6037621
PROJECTED ANSWERS: 23 TO 61

L7 7 SEA SSS FUL L6

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	175.25	529.16

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-0.78

FILE 'CAPLUS' ENTERED AT 16:51:32 ON 24 SEP 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 24 Sep 2007 VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007 (20070923/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s l7 full
L8 2 L7

=> d ibib abs hitstr tot

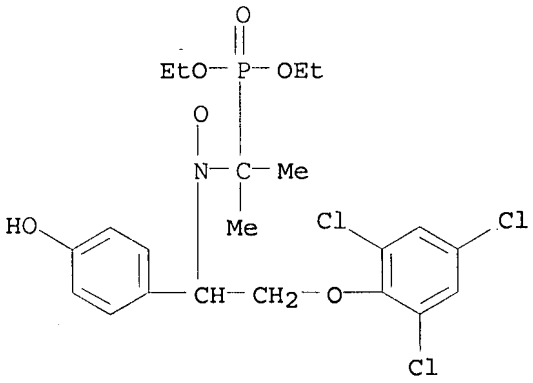
L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:908614 CAPLUS
DOCUMENT NUMBER: 145:454704
TITLE: Effect of the Phosphoryl Substituent in the Linear Nitrone on the Spin Trapping of Superoxide Radical and the Stability of the Superoxide Adduct: Combined Experimental and Theoretical Studies
AUTHOR(S): Liu, Yang-Ping; Wang, Lan-Fen; Nie, Zhou; Ji, Yi-Qiong; Liu, Yang; Liu, Ke-Jian; Tian, Qiu
CORPORATE SOURCE: State Key Laboratory for Structural Chemistry of Unstable and Stable Species, Center for Molecular

Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100080, Peop. Rep. China
SOURCE: Journal of Organic Chemistry (2006), 71(20), 7753-7762
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:454704

AB A new phosphorylated linear nitrone N-(4-hydroxybenzylidene)-1-diethoxyphosphoryl-1-methylethylamine N-oxide (4-HOPPN) was synthesized, and its X-ray structure was determined The spin trapping ability of various kinds of free radicals by 4-HOPPN was evaluated. Kinetic study of decay of the superoxide spin adduct (4-HOPPN-OOH) shows the half-life time of 8.8 min. On the basis of the X-ray structural coordinates, theor. analyses using d. functional theory (DFT) calcns. at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level were performed on spin-trapping reactions of superoxide radical with 4-HOPPN and PBN and three possible decay routes for their corresponding superoxide adducts. The comparative calcns. on the spin-trapping reactions with superoxide radical predicted that both spin traps share an identical reaction type and have comparable potency when spin trapping superoxide radical. Anal. of the optimized geometries of 4-HOPPN-OOH and PBN-OOH reveals that an introduction of the phosphoryl group can efficiently stabilize the spin adduct through the intramol. H-bonds, the intramol. nonbonding attractive interactions, as well as the bulky steric protection. Examination of the decomposition thermodn. of 4-HOPPN-OOH and PBN-OOH further supports the stabilizing role of the phosphoryl group to a linear phosphorylated spin adduct.

IT 913260-59-0
RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation, nonpreparative)
(effect of phosphoryl substituent in linear nitrone on spin trapping of superoxide radical and stability of superoxide)

RN 913260-59-0 CAPLUS
CN Nitroxide, 1-(diethoxyphosphinyl)-1-methylethyl 1-(4-hydroxyphenyl)-2-(2,4,6-trichlorophenoxy)ethyl (9CI) (CA INDEX NAME)



REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

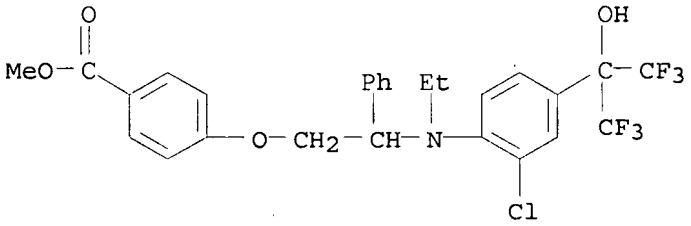
L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:874491 CAPLUS

DOCUMENT NUMBER: 145:471200
TITLE: Synthesis and evaluation of anilinohexafluoroisopropanols as activators/modulators of LXRα and β
AUTHOR(S): Panday, Narendra; Benz, Jorg; Blum-Kaelin, Denise; Bourgeaux, Vanessa; Dehmlow, Henrietta; Hartman, Peter; Kuhn, Bernd; Ratni, Hassen; Warot, Xavier; Wright, Matthew B.
CORPORATE SOURCE: Pharmaceuticals Division, Preclinical Research, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(19), 5231-5237
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:471200

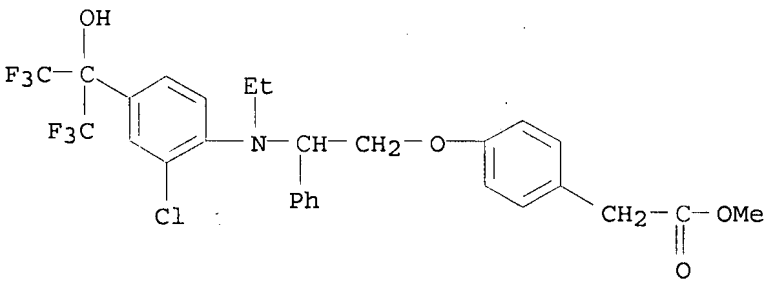
AB A series of branched and unbranched anilinohexafluoroisopropanols related to the known sulfonamide T0901317 were prepared and evaluated as activators/modulators of both LXRα and LXRβ. A structure-activity relationship was established and compds. with high potency on both the receptors were identified. Many compds. showed a tendency toward selectivity for LXRβ vs. LXRα. Several analogs were evaluated for effects on plasma lipoprotein levels in mice. A few of these significantly raised HDL-cholesterol levels in plasma but showed markedly different effects on liver triglyceride content, suggesting that this series may yield candidates with improved efficacy/safety profiles compared to existing mols.

IT 913619-59-7P 913619-60-0P 913619-61-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and evaluation of anilinohexafluoroisopropanols as activators/modulators of LXRα and β)

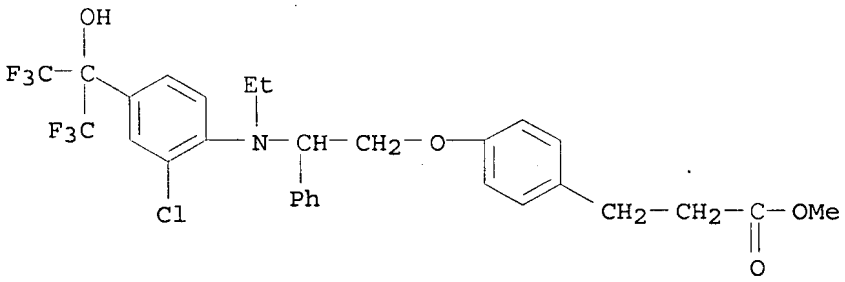
RN 913619-59-7 CAPLUS
CN Benzoic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]-, methyl ester (CA INDEX NAME)



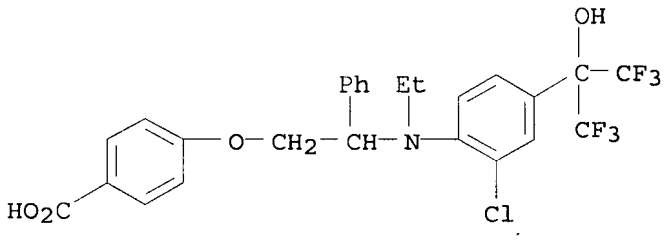
RN 913619-60-0 CAPLUS
CN Benzeneacetic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]-, methyl ester (CA INDEX NAME)



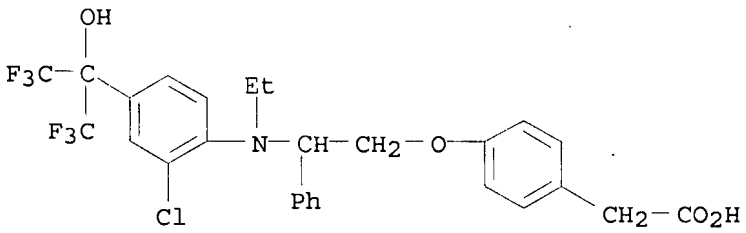
RN 913619-61-1 CAPLUS
CN Benzenepropanoic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]-, methyl ester (CA INDEX NAME)



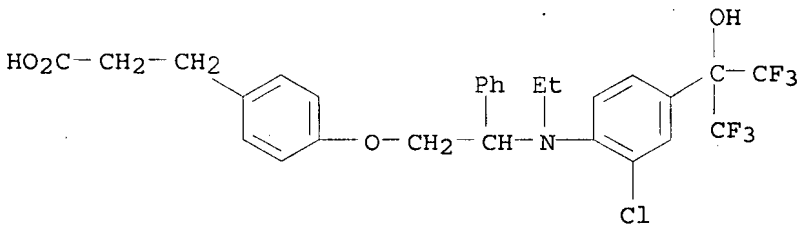
IT 913619-62-2P 913619-63-3P 913619-64-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and evaluation of anilinohexafluoroisopropanols as activators/modulators of LXRα and β)
RN 913619-62-2 CAPLUS
CN Benzoic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]- (CA INDEX NAME)



RN 913619-63-3 CAPLUS
CN Benzeneacetic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]- (CA INDEX NAME)



RN 913619-64-4 CAPLUS
CN Benzenepropanoic acid, 4-[2-[[2-chloro-4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]ethylamino]-2-phenylethoxy]- (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	12.89	542.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.56	-2.34

FILE 'REGISTRY' ENTERED AT 16:54:45 ON 24 SEP 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1
DICTIONARY FILE UPDATES: 23 SEP 2007 HIGHEST RN 947726-74-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of

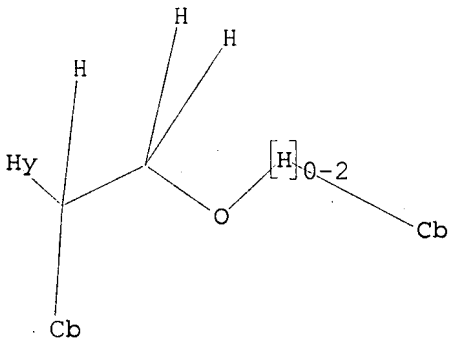
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\Stnexp\Queries\10599824last.str

L9 STRUCTURE UPLOADED

=> d l9
L9 HAS NO ANSWERS
L9 STR



G1 H,X,Ak,O

Structure attributes must be viewed using STN Express query preparation.

=> s l9 full
FULL SEARCH INITIATED 16:55:06 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 25530888 TO ITERATE

0.8% PROCESSED 200310 ITERATIONS 0 ANSWERS

1.6% PROCESSED 398021 ITERATIONS 0 ANSWERS

2.4% PROCESSED 605940 ITERATIONS 0 ANSWERS

3.5% PROCESSED 890366 ITERATIONS 0 ANSWERS

3.7% PROCESSED 932709 ITERATIONS 0 ANSWERS

3.9% PROCESSED 1000000 ITERATIONS 0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.01.38

FULL FILE PROJECTIONS: ONLINE **INCOMPLETE**
BATCH **INCOMPLETE**
PROJECTED ITERATIONS: 25530888 TO 25530888
PROJECTED ANSWERS: 0 TO 0

L10 0 SEA SSS FUL L9

=> d his

```
     (FILE 'HOME' ENTERED AT 16:41:51 ON 24 SEP 2007)

     FILE 'REGISTRY' ENTERED AT 16:41:58 ON 24 SEP 2007
L1             STRUCTURE UPLOADED
L2           1 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 16:42:31 ON 24 SEP 2007
               S L1

     FILE 'REGISTRY' ENTERED AT 16:42:39 ON 24 SEP 2007
L3           1 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 16:42:43 ON 24 SEP 2007
L4           1 S L3 FULL

     FILE 'CAPLUS' ENTERED AT 16:42:49 ON 24 SEP 2007
L5           1 S L2 FULL

     FILE 'REGISTRY' ENTERED AT 16:47:02 ON 24 SEP 2007
L6             STRUCTURE UPLOADED
L7           7 S L6 FULL

     FILE 'CAPLUS' ENTERED AT 16:51:32 ON 24 SEP 2007
L8           2 S L7 FULL

     FILE 'REGISTRY' ENTERED AT 16:54:45 ON 24 SEP 2007
L9             STRUCTURE UPLOADED
L10          0 S L9 FULL
```

Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 3195–3198

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Dual NK_1 Antagonists—Serotonin Reuptake Inhibitors as Potential Antidepressants. Part 2: SAR and Activity of Benzyloxyphenethyl Piperazine Derivatives†

Thomas Ryckmans,[a,*] Olivier Berton,[b] Renée Grimée,[b] Thierry Kogej,[a] Yves Lamberty,[b] Patrick Pasau,[a] Patrice Talaga[a] and Christophe Genicot[a]

[a]*Chemical Research, R&D, UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium*
[b]*Preclinical CNS Research, R&D, UCB Pharma SA, Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium*

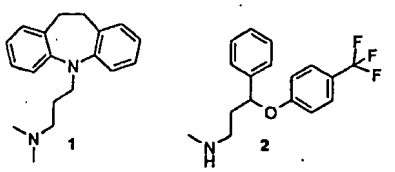
Received 24 May 2002; accepted 17 July 2002

Abstract—The synthesis, structure–affinity relationship and activity of benzyloxyphenethyl piperazine derivatives combining NK_1 antagonism and serotonin reuptake inhibition is described. Compound 7u was shown to be active in animal models of 5-HT reuptake inhibition and central NK_1 receptor blockade, and was demonstrated to be orally active in an integrated model sensitive to both mechanisms. This class of compounds potentially represents a new generation of antidepressants.

Depression is reported to affect up to 10% of the population[2] and is linked with a significant mortality. Antidepressant therapies using tricyclics (such as imipramine 1) or Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluoxetine 2 are efficacious in about 70% of patients but are associated with side effects such as dry mouth and blurred vision for tricyclics, and gastrointestinal distress, anxiety, insomnia and sexual dysfunction for the SSRIs.

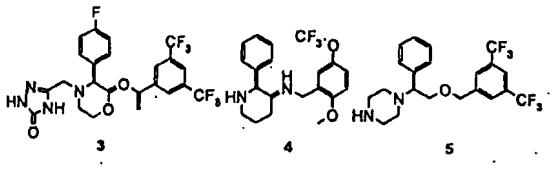
Another common problem in current therapies is their slow onset of action, since a delay of about 4 weeks is normally observed between the beginning of the treatment and alleviation of the symptoms. This delay appears to parallel the progressive desensitization of somatodendritic $5HT_{1A}$ receptors which in turn gradually increases serotoninergic function. Indeed, clinical evidence shows that co-administration of a $5\text{-}HT_{1A}$ antagonist such as pindolol has a beneficial effect on the onset of action of SSRIs.[3,4]

Several lines of research[4,5] are being pursued along these lines for the discovery of new antidepressants, as well as non-monoaminergic approaches such as estrogen,[6,7] CRF[8–14] and NK_1[15] receptor ligands (Scheme 1).



Scheme 1. First- and second-generation antidepressants.

Thus far, NK_1 antagonists[15–18] seem especially promising. Indeed, in an animal model of depression,[19] NK_1 antagonists have a faster onset of action than imipramine (1). In clinical trials, two NK_1 antagonists, MK-869[16] (3) and CP 122,721[20,21] (4) were reported to have robust efficacy in treating depression (Scheme 2).



Scheme 2. NK_1 antagonists: MK-869, CP 122,721 and compound 5.

†For Part I, see ref 1.

*Corresponding author at present address: Department of Discovery Chemistry, Pfizer Global Research and Development ipc 432, Sandwich, Kent CT13 9NJ, UK. Tel.: +44-1304-643-735; fax: +44-1304-651-987; e-mail: thomas_ryckmans@sandwich.pfizer.com

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00563-2

The mode of action of NK_1 antagonists is now believed to involve an indirect modulation of 5-HT function, via Noradrenergic pathways.[22,23] NK_1 receptor knock-out mice and wild-type mice treated with NK_1 antagonists have an attenuated presynaptic $5HT_{1A}$ receptor function.[23–25] The combination of serotonin reuptake inhibition with NK_1 antagonism (modulating $5HT_{1A}$ function) may thus lead to a new class of antidepressants with an improved onset of action and better efficacy.

The optimisation of a family of phenoxyacetamides with dual affinities for the NK_1 receptor and the Serotonin Reuptake Site has recently been reported,[1] while Merck has described in the patent literature compounds claimed to have a similar profile.[26] We now report the SAR and in vivo activity of benzyloxyphenethyl piperazine derivatives that similarly combine Serotonin Reuptake Inhibition and NK_1 antagonism.

Screening[27–29] of NK_1 antagonists from the UCB compound collection against the Serotonin Transporter (ST) resulted in the identification, amongst others, of compound **5** (Table 1), which displays excellent affinity for the NK_1 receptor but moderate affinity for the ST. This compound was used as a starting point for this work.

Chemistry

The key alcohols **6** were prepared by either substitution of a bromo phenylacetic ester with the Boc-protected piperazine followed by reduction, or by an efficient, three component reaction[30,31] between an arylboronic acid, glycolaldehyde and the Boc-protected piperazine. Enantiopure **6** were prepared by reaction of homochiral phenylglycinols with the activated *N*-tosyl diethanolamine derivative. Alcohols **6** were then *O*-benzylated and deprotected to afford the corresponding compounds **7** in racemic (**7a–q**) or enantiopure (**7r–u**) form (Scheme 3).

Table 1. Affinities of compounds 2–7 for the NK_1 receptor and the Serotonin Transporter (ST)

Compd (configuration)	R_1	R_2	pIC_{50} NK_1[a]	pIC_{50} ST[a]
2 fluoxetine	—	—	—[b]	8.2
3 MK 869	—	—	10.0[c]	—
5	—	3′, 5′-di CF_3	8.3	6.6
7a	4-F	3′, 5′-di CF_3	7.0	6.8
7b	4-OMe	3′, 5′-di CF_3	7.3	7.0
7c	3-Cl	3′, 5′-di CF_3	8.8	6.6
7d	3-iPr	3′, 5′-di CF_3	7.4	6.5
7e	3-OMe	3′, 5′-di CF_3	9.0	6.7
7f	2-F	3′, 5′-di CF_3	8.3	6.7
7g	2-Cl	3′, 5′-di CF_3	8.8	6.7
7h	2-OMe	3′, 5′-di CF_3	8.2	6.6
7i	3,4-di Cl	3′, 5′-di CF_3	8.3	6.7
7j	2,3-di F	3′, 5′-di CF_3	8.5	6.5
7k	—	3′, 5′-di Me	7.6	—[d]
7l	—	3′, 5′-di ^{t}Bu	7.0	6.0
7m	—	3′-Cl	6.4	8.1
7n	—	3′, 5′-di F	6.7	9.1
7o	—	3′-CF_3, 5′-F	7.9	7.8
7p	—	3′-Br, 5′-I	8.9	7.6
7q	—	1′-OMe, 3′, 5′-di Br	8.1	8.2
7r (*R*)	—	3′, 5′-di Cl	7.6	7.9
7s (*S*)	—	3′, 5′-di Cl	8.5	8.6
7t (*R*)	—	3′, 5′-di Br	7.9	7.5
7u (*S*)	—	3′, 5′-di Br	8.5	8.0

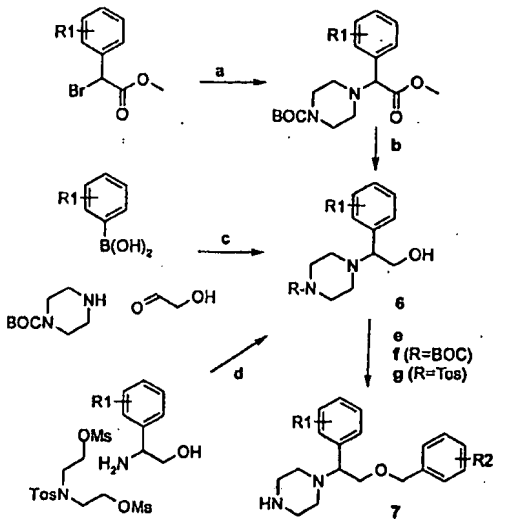
[a]Values are means of two experiments.
[b]Less than 50% inhibition at 10^{-5} M.
[c]See ref 32.
[d]Not tested.

Results

Modification of R_1 while keeping R_2 substitution constant showed that the NK_1 receptor does not tolerates 4-substituents while affinities for the ST were slightly improved (**7a**, **7b**). Substitution of the 3-position with chloro- or methoxy- was beneficial to NK_1r binding (**7c**, **7e**) but affinities for the ST were unaffected. Finally 2-substitution with a chloro group (**7g**) was found to improve affinities for the NK_1r but again left affinities for the ST unchanged. 3,4- and 2,3-Disubstitutions were not beneficial (**7i**, **7j**). We then turned to modification of R_2 in order to improve affinity for the ST.

Substitution with small (**7k**) or large (**7l**) alkyl groups led to an overall loss of affinities. Monosubstitution (**7m**) or disubstitution with the smaller fluoro atoms (**7n**) led to an important reduction of the affinities toward NK_1r while ST binding was greatly improved. Unsymmetrical disubstitution with the 3′-CF_3, 5′-F (**7o**) or 3′-bromo 5′-iodo (**7p**) provided compounds with high affinities for both targets. Trisubstitution (**7q**) was also beneficial.

At this stage, enantiopure compounds bearing the 3′,5′-dichloro and 3′,5′-dibromo substitution (**7r–7u**) were prepared. Fortunately, in each case, the *S* enantiomers displayed very high affinities toward both targets, while



Scheme 3. Preparation of benzyloxyphenethyl piperazines: (a) BOC-piperazine, K_2CO_3, DMF, rt; (b) $LiBH_4$, THF, reflux; (c) CH_2Cl_2, rt; (d) Et_3N, DMF, 80 °C; (e) NaH, THF, Benzyl bromide, NaI, 60 °C; (f) TFA–CH_2Cl_2; (g) AcOH–HBr, 90 °C.

102(b)

the *R* enantiomers proved to be inferior. Compounds 7s and 7u were selected for further examination in vivo.

To assess the central 5-HT reuptake blockade properties of the compounds, we tested their ability to increase extracellular 5-HT levels in the frontal cortex of freely moving rats by using intracerebral microdialysis.[33] Intraperitoneal administration of **7u** (3.2×10^{-5} mol/kg, $n=2$) increased 5-HT levels up to 250% of baseline for more than 3 h. In this model, 7s was found to be poorly active, possibly because of metabolic instability or limited brain penetration. Activity of **7u** as a NK_1 antagonist was assessed using the gerbil foot-tapping model as described by Rupniak.[34] At the dose of 3.2×10^{-5} mol/kg (ip, $n=5$), **7u** decreased by 45% the duration of the foot-tapping, indicating efficacious central blockade of NK_1 receptors. Finally, in the isolation-induced guinea pig pup vocalization test, an integrated behavioural model sensitive to both SSRI and NK_1 antagonists,[35] **7u** was shown to be orally active, as it was able to attenuate by 50% (1×10^{-5} mol/kg, $n=8$) and 99% (3.5×10^{-5} mol/kg, $n=8$) the duration of vocalizations.

In conclusion, we were able to optimise a family of benzyloxyphenethyl piperazines to the level of fluoxetine for the ST, with an added affinity for the NK_1 receptor. One of the best compounds in this family was shown to be active in animal models indicative of 5-HT reuptake inhibition and central NK_1 receptor blockade, and was demonstrated to be orally active in an validated animal model of depression sensitive to both mechanisms.

Further developments in this area will be reported in due course.

Acknowledgements

The authors wish to thank Marie-Agnes Lassoie for initial preparation of racemic 7t–u, Reiner Dieden and Alain Fauconnier for their skillful analytical assistance, Bruno Fuks and Michel Gillard for the in vitro binding measurements, Corinne Audouin for follow-up of the manuscript and Luc Quéré for fruitful discussions.

References and Notes

1. Ryckmans, T.; Balançon, L.; Berton, O.; Genicot, C.; Lamberty, Y.; Lallemand, B.; Pasau, P.; Pirlot, N.; Quéré, L.; Talaga, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 261.
2. Kerrigan, F. *Exp. Opin. Ther. Pat.* **1998**, *8*, 439.
3. Arborelius, L. *I Drugs* **1999**, *2*, 121.
4. Artigas, F.; Romero, L.; de Montigny, C.; Blier, P. *Trends Neurosci.* **1996**, *19*, 378.
5. Briner, K.; Dodel, R. C. *Curr. Pharm. Des.* **1998**, *4*, 291. For a recent example, see: Mewshaw, R. E.; Meagher, K. L.; Zhou, P.; Zhou, D.; Shi, X.; Scerni, R.; Smith, D.; Schechter, L. E.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 307.
6. McEwen, B. S.; Alves, S. E. *Endocr. Rev.* **1999**, *20*, 279.
7. Schopfer, U.; Schoeffter, P.; Bischoff, S.; Nozulak, J.; Feuerbach, D.; Floersheim, P. *J. Med. Chem.* **2002**, *45*, 1399.
8. Arborelius, L.; Owens, M. J.; Plotsky, P. M.; Nemeroff, C. B. *J. Endocrinol.* **1999**, *160*, 1.
9. Dautzenberg, F. M.; Hauger, R. L. *Trends Pharmacol. Sci.* **2002**, *23*, 71.
10. Gilligan, P. J.; Robertson, D. W.; Zaczek, R. *J. Med. Chem.* **2000**, *43*, 1641.
11. Hodge, C. N.; Aldrich, P. E.; Wasserman, Z. R.; Fernandez, C. H.; Nemeth, G. A.; Arvanitis, A.; Cheeseman, R. S.; Chorvat, R. J.; Ciganek, E.; Christos, T. E.; Gilligan, P. J.; Krenitsky, P.; Scholfield, E.; Strucely, P. *J. Med. Chem.* **1999**, *42*, 819.
12. McCarthy, J. R.; Heinrichs, S. C.; Grigoriadis, D. *Ann. Rep. Med. Chem.* **1999**, *34*, 11.
13. McCarthy, J. R.; Heinrichs, S. C.; Grigoriadis, D. E. *Curr. Pharm. Des.* **1999**, *5*, 289.
14. Saunders, J.; Williams, J. P. *Ann. Rep. Med. Chem.* **2001**, *36*, 21.
15. Rupniak, N. M. *Curr. Opin. Investig. Drugs* **2002**, *3*, 257. See also: Baby, S.; Nguyen, M.; Tran, D.; Raffa, R. B. *J. Clin. Pharm. Ther.* **1999**, *24*, 461.
16. Kramer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Swain, C. J.; Harrison, T.; Hill, R. G.; Hefti, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Rupniak, N. M. *Science* **1998**, *281*, 1640.
17. Kramer, M. S. *Neuropeptides* **2000**, *34*, 255.
18. Maubach, K. A.; Rupniak, N. M.; Kramer, M. S.; Hill, R. G. *Curr. Opin. Chem. Biol.* **1999**, *3*, 481.
19. Papp, M.; Vassout, A.; Gentsch, C. *Behav. Brain Res.* **2000**, *115*, 19.
20. Rosen, T. J.; Coffman, K. J.; McLean, S.; Crawford, R. T.; Bryce, D. K.; Gohda, Y.; Tsuchiya, M.; Nagahisa, A.; Nakane, M.; Lowe, J. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 281.
21. *CNS Drug News* **2000**, December, 24.
22. Haddjeri, N.; Blier, P. *NeuroReport* **2000**, *11*, 1323.
23. Santarelli, L.; Gobbi, G.; Debs, P. C.; Sibille, E. T.; Blier, P.; Hen, R.; Heath, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 1912.
24. Oficialdegui, A. M.; Martinez, J.; Perez, S.; Heras, B.; Irurzun, M.; Palop, J. A.; Tordera, R.; Lasheras, B.; del Rio, J.; Monge, A. *Farmaco* **2000**, *55*, 345.
25. Froger, N.; Gardier, A. M.; Moratalla, R.; Alberti, I.; Lena, I.; Boni, C.; de Felipe, C.; Rupniak, N. M.; Hunt, S. P.; Jacquot, C.; Hamon, M.; Lanfumey, L. *J. Neurosci.* **2001**, *21*, 8188.
26. MacLeod, A. M.; Swain, C. J.; van Niel, M. B. US Patent 6,136,824, 2000.
27. Marcusson, J. O.; Bergstrom, M.; Eriksson, K.; Ross, S. B. *J. Neurochem.* **1988**, *50*, 1783.
28. Aharony, D.; Catanese, C. A.; Woodhouse, D. P. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 146.
29. Affinity of the test compounds for the ST was evaluated by a [^{3}H]paroxetine binding assay. This binding was performed as described by Marcusson et al.[27] with slight modifications. 100–200 μg of membrane proteins from rat cerebral cortex were incubated for 120 min at 25 °C in 2 mL of a 50 mM Tris–HCl (pH 7.4) buffer containing 2 mM $MgCl_2$ and 0.05 nM radioligand. Non specific binding defined as the residual binding was measured in the presence of 5 μM Imipramine. The affinity of the test compounds for the human NK_1 receptor was measured as described by Aharony et al.[28] Briefly, 10–20 μg of membrane proteins from CHO cells expressing the human NK_1 receptor were incubated for 60 min at 25 °C in 0.5 mL of the same buffer as above, supplemented with 100 μg/mL bacitracine and 0.25 nM [^{3}H]substance P. The non specific binding was measured in the presence of 1 μM CP-96345.
30. Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **2002**, *53*, 16463.
31. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

32. Hale, J. J.; Mills, S. G.; MacCoss, M.; Dorn, C. P.; Finke, P. E.; Budhu, R. J.; Reamer, R. A.; Huskey, S. E.; Luffer-Atlas, D.; Dean, B. J.; McGowan, E. M.; Feeney, W. P.; Chiu, S. H.; Cascieri, M. A.; Chicchi, G. G.; Kurtz, M. M.; Sadowski, S.; Ber, E.; Tattersall, F. D.; Rupniak, N. M.; Williams, A. R.; Rycroft, W.; Hargreaves, R.; Metzger, J. M.; MacIntyre, D. E. *J. Med. Chem.* **2000**, *43*, 1234.

33. Sharp, T.; Zetterström, T. In *Monitoring Neural Activity*; Oxford University Press: New York, 1992; p 147.

34. Rupniak, N. M.; Williams, A. R. *Eur. J. Pharmacol.* **1994**, *265*, 179.

35. Rupniak, N. M.; Carlson, E. C.; Harrison, T.; Oates, B.; Seward, E.; Owen, S.; de Felipe, C.; Hunt, S.; Wheeldon, A. *Neuropharmacology* **2000**, *39*, 1413.